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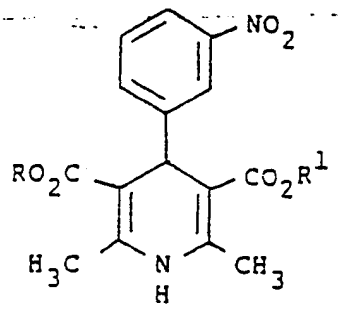
(54) Stabilized pharmaceutical compositions.

(57) Stabilized solid pharmaceutical preparations containing, as active ingredient, a 1,4-dihydropyridine derivative of formula:



(in which R is an n-propyl group substituted at the 2-or 3-position with a nitrato group and R^1 is a 2-nitratoethyl group which may be substituted with a methyl group at the 1- or 2-position) and one or more pharmaceutical auxiliary agents, in which the composition also contains as stabilizer, one or more of sodium carbonate, sodium hydrogen carbonate, calcium carbonate and calcium hydrogen phosphate.

EP 0 264 259 A1

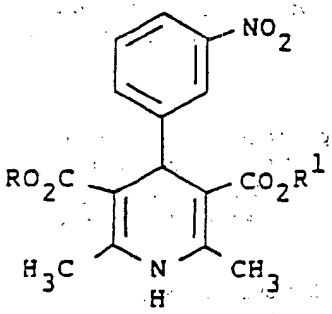
Description

STABILIZED PHARMACEUTICAL COMPOSITIONS

The present invention relates to stabilized pharmaceutical compositions and, more particularly, is concerned with stabilized therapeutic compositions for the treatment of circulatory diseases and containing a dihydropyridine derivative as an active ingredient.

The dihydropyridine derivatives used as active ingredients in the compositions of the invention are disclosed in Japanese Laid-Open Patent No. 60-89420. These dihydropyridine derivatives tend to decompose, to a large extent, in solid pharmaceutical preparations and thus long-term storage of such preparations is a problem.

According to the invention there is provided a solid pharmaceutical composition containing, as active ingredient, a 1,4-dihydropyridine derivative of the formula:



(I)

(in which R is an n-propyl group substituted at the 2-or 3-position with a nitrato group and R^1 is a 2-nitratoethyl group which may be substituted with a methyl group at the 1- or 2-position) together with one or more pharmaceutical auxiliary agents, characterized in that the composition also contains one or more of sodium carbonate, sodium hydrogen carbonate, calcium carbonate and calcium hydrogen phosphate.

The invention also provides a method of stabilizing a solid pharmaceutical composition containing, as active ingredient, a 1,4-dihydropyridine derivative of formula (I), which method comprises incorporating, in the composition, one or more of sodium carbonate, sodium hydrogen carbonate, calcium carbonate and calcium hydrogen phosphate.

Sodium carbonate, sodium hydrogen carbonate and/or calcium carbonate when used in the invention are suitably present in an amount of from 0.01 to 20 parts by weight, preferably from 0.01 to 10 parts by weight, per part by weight of the compound of formula (I). Calcium hydrogen phosphate, when used, is suitably present in an amount of from 0.01 to 100 parts by weight, preferably from 0.1 to 80 parts by weight, per part by weight of the compound of formula (I).

The stabilized compositions of the invention can be prepared by any suitable conventional means. Thus, for example, there may be added to the compound of formula (I) one or more of sodium carbonate, sodium hydrogen carbonate, calcium carbonate and calcium hydrogen phosphate, followed by addition of pharmaceutical auxiliary agents such as excipients, lubricants and disintegrants, if required. A variety of pharmaceutical preparations, such as powders, tablets, capsules and granules, can be formed from the resultant mixture.

Suitable excipients for use in the compositions of the invention are lactose, corn starch and/or mannitol, and these are suitably used in amounts of from 0.1 to 90% by weight, preferably from 10 to 60% by weight, based on the total weight of the composition.

Suitable disintegrants are low substituted hydroxypropyl celluloses (suitably used in an amount of 0.1 - 30% by weight, preferably 10-25% by weight), calcium carboxymethyl cellulose (suitably used in an amount of 0.1-20% by weight, preferably 1-10%): hydrogenated oil (suitably used in an amount of 0.1-10% by weight, preferably 1-5% by weight); and talc (suitably used in an amount of 0.1 - 20% by weight, preferably 2-10% by weight).

In order that the invention may be well understood the following examples are given by way of illustration only.

Example 1

One gram of 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2-nitratoethyl) ester 5-(3-nitratopropyl) ester [general formula (I): R= $-CH_2CH_2ONO_2$, R^1= $-CH_2CH_2CH_2ONO_2$, "Compound A"], 27 g of lactose, 70 g of calcium hydrogen phosphate and 2 g of talc were uniformly blended and passed through a 42-mesh screen to give powders which were divided into 1-g packs.

Example 2

Two grams of 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2-nitratopropyl) ester 5-(3-nitratopropyl) ester [general formula (I): R=$-CH_2CH_2CH_2ONO_2$, R^1= $-CH_2CH(CH_3)ONO_2$;

"Compound B"], 30 g of corn starch, 59 g of mannit, 5 g of calcium carbonate and 4 g of lubriwax were uniformly blended and passed through a 42-mesh screen to give powders which were divided into l-g packs.

Example 3

Three grams of 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(1-methyl-2-nitrato-ethyl) ester 5-(3-nitratopropyl) ester [general formula (I): R = $-CH_2CH_2ONO_2$, $R^1 = -CH(CH_3)CH_2ONO_2$; "Compound C" 25 g of corn starch, 62 g of lactose, 5 g of sodium hydrogen carbonate and 5 g of talc were uniformly blended and passed through a 42-mesh screen to give powders which were divided into 1-g packs.

Example 4

Four grams of 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid bis(2-nitratopropyl) ester [general formula (I) $R = R^1 = -CH_2CH(CH_3)ONO_2$; "Compound D"], 74.5 g of corn starch, 10 g of a low substituted hydroxypropylcellulose (LHPC) and 4 g of sodium carbonate were uniformly and then kneaded together with an appropriate amount of water employing 5 g of hydroxypropylcellulose (HPC) as a binder followed by granulation in a bascket granulator. The granules were dried and mixed with 2.5 g of hydrogenated oil to give granules which were divided into 1-g packs.

Example 5.

Five grams of Compound A, 36 g of lactose, 45 g of mannitol, 1 g of calcium carboxymethylcellulose (called CMC-Ca hereinbelow) and 2 g of sodium carbonate were uniformly blended and kneaded together with an appropriate amount of water by employing 5 g of HPC as a binder followed by drying and granulation. To the granules was added 6 g of talc followed by mixing to give granules which were divided into 1-g packs.

Example 6.

Six grams of Compound B, 20 g of corn starch, 36 g of lactose, 25 g of LHPC and 5 g of sodium carbonate were uniformly blended and kneaded together with an appropriate amount of water employing 5 g of HPC as a binder followed by drying and granulation. The granules were mixed with 3 g of hydrogenated oil to give granules which were divided into 1-g packs.

Example 7.

Twenty grams of Compound C, 12 g of lactose, 10 g of mannitol, 3 g of CMC-Ca and 40 g of calcium hydrogen phosphate were uniformly blended. From the blend were prepared wet granules employing 5 g of HPC as a binder in a conventional manner. The granules were dried, mixed with 10 g of talc and formed into granules. The resulting granules were tableted by the granule-compression method to give tablets each 8 mm in diameter and weighing 200 mg.

Example 8.

Fifteen grams of Compound D, 65.5 g of mannitol, 15 g of LHPC, 1 g of calcium carbonate and 3.5 g of lubriwax were uniformly blended and directly tableted into tablets each 7 mm in diameter and weighing 150 mg.

Example 9.

Thirty grams of Compound A, 45 g of corn starch, 5 g of CMC-Ca, 7 g of sodium carbonate and 5 g of HPC were uniformly blended and granulated by the dry granulation method. To the granules thus prepared were added 8 g of talc. The mixtures were tableted by the granule-compression method to give tablets each 6 mm in diameter and weighing 100 mg.

Example 10.

Ten grams of Compound B, 30 g of corn starch, 33 g of mannitol, 15 g of LHPC, 5 g of sodium hydrogen carbonate and 5 g of HPC were uniformly blended and kneaded together with an appropriate amount of water followed by mixing with 2 g of hydrogenated oil. The mixture was filled in gelatin capsules each containing 200 mg to give hard capsules.

Example 11.

Twenty grams of Compound C, 20 g of corn starch, 31 g of mannitol, 10 g of CMC-Ca, 10 g of sodium carbonate and 5 g of HPC were uniformly blended and kneaded together with an appropriate amount of water followed by drying and mixing with 4 g of talc. The mixture was filled in gelatin capsules each containing 100 mg to give hard capsules.

Example 12.

Twelve grams of Compound D, 48 g of mannitol, 20 g of LHPC 10 g of calcium hydrogen phosphate and 5 g of HPC were uniformly blended and formed into dry granules by the dry-granulation method. The granules were mixed with 5 g of hydrogenated oil. The mixture was filled in gelatin capsules each containing 240 mg to give hard capsules.

Example 13.

Ten grams of Compound B, 25 g of corn starch, 15 g of LHPC, 7 g of HPC and 40 g of calcium hydrogen phosphate were uniformly blended and kneaded together with an appropriate amount of water followed by mixing with 3 g of hydrogenated oil. The mixutre was formed by the granule-compression method into tablets each 8 mm in diameter and weighing 200 mg.

Test Example 1.

Pharmaceutical preparations prepared in Examples 2, 6, 10 and 13, which were named Preparations 2, 6, 10 and 13, respectively were placed in 20-cc brown bottles which were closed and stored in a thermostat at 65° ± 2°C for 14 days or at 50° ± 20°C for 60 days. The resulting samples were analyzed by high performance liquid chromatography for said compounds. Comparison was made with the data prior to storage in the thermometer to calculate remaining ratio.

$$\text{Remaining ratio (\%)} = \frac{\text{Analytical value for said compound after aged at 65°C ± 2°C for 14 days or at 50° ± 2°C for 60 days}}{\text{Analytical value for said compound prior to storage in the thermometer}} \times 100$$

Results are shown in Table 1.

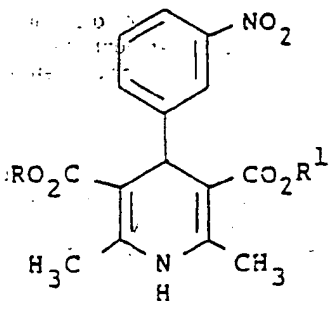
Control preparation was the same preparation as in Example 6 except for removal of the sodium carbonate.

Table 1

Preparation NO.	Remaining ratio of Compound B (%)	
	65°±2°C, 14 days	50°±2°C, 60 days
2	78.0	81.4
6	62.4	80.0
10	82.4	89.9
13	80.6	88.9
control	7.4	7.9

Claims

1. A solid pharmaceutical composition containing, as active ingredient, a 1,4-dihydropyridine derivative of the formula:



(I)

(in which R is an n-propyl group substituted at the 2-or 3-position with a nitrato group and R^1 is a 2-nitratoethyl group which may be substituted with a methyl group at the 1-or 2-position) and one or more pharmaceutical auxiliary agents, characterized in that the composition also contains, as stabilizer, one or more of sodium carbonate, sodium hydrogen carbonate, calcium carbonate and calcium hydrogen phosphate.

2. A composition as claimed in claim 1 characterized in that the sodium carbonate, sodium hydrogen carbonate and/or calcium carbonate is present in an amount of from 0.01 to 20 parts by weight per part by weight of the 1,4-dihydropyridine derivative.

3. A composition as claimed in claim 1 characterized in that the calcium hydrogen phosphate is present in an amount of from 0.01 to 100 parts by weight per part by weight of the 1,4-dihydropyridine derivative.

4. A method for stabilizing a solid pharmaceutical composition containing, as active ingredient, a 1,4-dihydropyridine derivative of formula (I) as defined in claim 1 characterized in that it comprises incorporating in the composition one or more of sodium carbonate, sodium hydrogen carbonate, calcium carbonate and calcium hydrogen phosphate.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 30 9038

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	PATENT ABSTRACTS OF JAPAN, vol. 10, no. 258 (C-370)[2314], 4th September 1986; & JP-A-61 83 123 (TAISHO PHARMACEUT CO LTD) 26-04-1986 * Abstract * ---	1-4	A 61 K 31/44 A 61 K 9/20 A 61 K 47/00
Y	EP-A-0 164 588 (BAYER AG) * Page 4, lines 5-7,12-14; page 6, lines 21-23; page 9, examples 1,2 * ---	1,3,4	
Y	EP-A-0 159 735 (DAGRA N.V.) * Page 3, lines 9-11; claims 1-4 * ---	2	
A	PATENT ABSTRACTS OF JAPAN, vol. 10, no. 131 (C-346)[2188], 15th May 1986; & JP-A-60 255 719 (TAKADA SEIYAKU K.K.) 17-12-1985 * Abstract * ---	1-4	
A	EP-A-0 168 789 (TAISHO PHARMACEUTICAL CO., LTD) * Whole document, especially page 12, lines 23-26 * -----	1-4	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K
C 07 D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	18-01-1988	FOERSTER W.K.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
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